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Clinical value of soluble suppression of tumourigenicity 2 (sST2) in addition to NTproBNP measurements in a general cardiac outpatient population

Ammann Camille[a], Wyss Christophe[b], Gämperli Oliver[b], Wenaweser Peter Martin[b], Corti Roberto[b], Noll Georg[b], Biaggi Patric[b]

[a] University of Zurich, Switzerland
[b] The Heart Clinic Hirslanden, Zurich, Switzerland

Summary

BACKGROUND AND AIMS: The soluble form of suppression of tumourigenicity 2 (sST2), a recently introduced biomarker, is a strong and NTproBNP-independent predictor of outcome in heart failure patients. This study sought to evaluate the added clinical value of sST2 in addition to NTproBNP in a heterogeneous cardiac outpatient population.

METHODS: A total of 297 all-comer patients visiting the outpatient clinic of Heart Clinic Zurich, Switzerland, from January to December 2018 were included. Patients were divided into four groups depending on their sST2 and NTproBNP levels: group 1 (n = 91, 30.6% of all patients) with normal levels of both biomarkers, group 2 (n = 41, 13.8%) with isolated elevation of sST2 but normal NTproBNP, group 3 (n = 97, 32.7%) with elevated NTproBNP but normal sST2 levels, and group 4 (n = 68, 22.9%) with elevation of both biomarkers. Differences between groups, Spearman's correlations and linear and multiple regression analysis for sST2 were calculated.

RESULTS: The median age was 74 ± 19 years and 41.8% were women. NTproBNP levels continuously increased across the groups (medians in pg/ml: group 1 123.0, group 2 152.0, group 3 990.0 and group 4 2610.0), whereas sST2 levels did not (medians in ng/ml: 28.7, 58.9, 28.4 and 63.7 for groups 1 to 4, respectively). In patients with normal NTproBNP (groups 1 and 2), elevation of sST2 (group 2) was associated with significantly higher rates of coronary artery disease, peripheral vascular disease and renal dysfunction. In patients with elevated NTproBNP (groups 3 and 4), the additional elevation of sST2 (group 4) was associated with clinical signs of heart failure, higher EuroScore II and worse left ventricular ejection fraction (LVEF group 3 58.0% vs group 4 53.3%, p = 0.022). Correlation of sST2 was overall weak and weaker than of NTproBNP with most clinical variables. Soluble ST2 significantly correlated with EuroScore II (R = 0.280), kidney function (R = −0.259), C-reactive protein (R = 0.248), right ventricular function (R = 0.213) and left atrial volume (R = 0.199), all p ≤0.001. In multiple regression analysis, left atrial volume was the strongest independent predictor of sST2 elevation (p = 0.002).

CONCLUSION: In this all-comer cardiology population, the added clinical value of sST2 measurements in addition to NTproBNP was small. In patients with elevated NTproBNP, the simultaneous elevation of sST2 was associated with clinical signs of heart failure. Soluble ST2 measurements could thus be beneficial in patients with uncertain signs of heart failure and confounding factors for NTproBNP elevation. Surprisingly, this study found elevated sST2 levels in a substantial number of a patients with normal NTproBNP levels, pointing to an additional pathway of sST2 elevation independent of heart failure.

Keywords: *Soluble ST2*, *NTproBNP*, *cardiac biomarkers*, *heart failure*

ABBREVIATIONS

BNP	Brain/b-type natriuretic peptide
HFmrEF	heart failure with mid-range ejection fraction (40–49%), heart failure symptoms, pathological NTproBNP, diastolic dysfunction
HFpEF	heart failure with preserved ejection fraction (≥50%), heart failure symptoms, pathological NTproBNP, diastolic dysfunction
HFrEF	heart failure with reduced ejection fraction (<40%), heart failure symptoms
LAVi	left atrial volume index
LVEF	left ventricular ejection fraction
MAP	mean arterial pressure = (2/3)*BP(diast) + (1/3)*BP(syst)
NTproBNP/NTpBNP	N-terminal pro-brain natriuretic peptide
sST2	soluble ST2
ST2	suppression of tumourigenicity 2

Disclaimer
The views in this article are the authors' view and do not represent an official position of The Heart Clinic Zurich or the study's funders.

Correspondence:
PD Dr med. Patric Biaggi, HerzKlinik Hirslanden, Witellikerstrasse 40, CH-8032 Zürich, patric.biaggi[at]hirslanden.ch

Introduction

Biomarkers form an essential pillar in the detection, management and prognosis of cardiac disease. The natriuretic peptide BNP and its cleavage product N-terminal pro-brain natriuretic peptide (NTproBNP), representing myocardial wall stretch and therefore the presence of cardiac stress, help in the differential diagnosis of dyspnoeic patients in the emergency room [1]. Apart from this acute setting, natriuretic peptides have become a standard follow-up parameter in patients with chronic cardiac disease. They correlate with the disease's clinical presentation (e.g., New York Heart Association dyspnoea scale) [2], respond to efficient treatment and have prognostic power in various cardiac diseases [3, 4]. However, natriuretic peptides have their limitations. BNP and NTproBNP are strongly dependent on a patient's age and comorbidities such as renal dysfunction and atrial fibrillation [5–8]. This renders their interpretation in elderly, multimorbid patients difficult.

The newly introduced cardiac biomarker soluble ST2 (suppression of tumourigenicity 2) has been identified as less dependent on previously named cofactors [9].

ST2 is a transmembrane receptor in cardiac myocytes and fibroblasts and binds interleukin-33. Interleukin-33 is secreted by cardiac fibroblasts and myocytes in response to cyclic biomechanical strain, cell damage, inflammation and a number of still-to-be identified stimuli [10]. The binding of interleukin-33 to the transmembrane ST2 receptor activates cardioprotective pathways that suppress adverse cardiac remodelling, such as hypertrophy and fibrosis [11]. The soluble form of ST2 (sST2), which is secreted by the same cells and in response to the same triggers as interleukin-33, competes with the transmembrane receptor form for binding with interleukin-33, inducing adverse cardiac remodelling [12]. Elevated sST2 levels are associated with various diseases causing cardiac fibrosis and remodelling, and the experimental injection of sST2 in animal models results in phenotypes with myocardial hypertrophy, ventricular dilatation and reduced cardiomyocyte contractility [13].

Soluble ST2 has been proven a powerful predictor of rehospitalisation and death in hospitalised patients with acute or chronic heart failure (both with reduced [14–18] and preserved ejection fraction [19]). Established ways of using sST2 in clinical practice are: (1) in acute decompensated heart failure: monitoring sST2 levels during hospitalisation. Patients with persistently high levels at discharge are at risk for early rehospitalisation. (2) In ambulatory heart failure clinics: measuring sST2 levels before and after treatment. Effective therapy is said to decrease sST2 values [10].

The presentation of sST2 in an outpatient all-comer setting and its additional value and relationship with the gold standard cardiac biomarker NTproBNP has been less explored in the past. The goal of this study was to observe the behaviour of sST2 in relation to cardiac function, symptomatology and comorbidities, and to better understand its added value when routinely measured in combination with NTproBNP in a heterogeneous outpatient population.

Methods

Study population

We performed a single-centre, cross sectional observational study of a heterogeneous all-comer group of patients visiting the outpatient clinic of Heart Clinic Hirslanden, Zurich, Switzerland from January to December 2018. All patients agreeing to the written general consent form, older than 18 years and with an indication for measuring cardiac biomarkers were included. Patient visits were scheduled for screening, initial, follow-up or emergency consultations for heart disease. Clinical information, laboratory variables and echocardiographic data were gathered from medical charts. Gender was determined according to the participant's statement. Echocardiographic examinations were performed according to current guidelines [20]. EuroScore II mortality risk was calculated for the same hypothetical cardiac surgery in all participants, namely an elective isolated coronary artery bypass graft without surgery on the thoracic aorta. Heart failure was classified into heart failure with reduced, mid-range and preserved ejection fraction according to the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure [21]. The protocol of this study was approved by the cantonal ethics comity of Zurich (Kantonale Ethikkommission Zürich, BASEC-Nr. 2018-00749) and complies with the Declaration of Helsinki.

Biomarkers

Blood samples for measurement of sST2 and NTproBNP were collected from every participant at the time of consultation. Plasma NTproBNP was measured using a sandwich immunoassay (proBNP II; Roche Diagnostics, Rotkreuz) with a reporting-range of 25–35,000 pg/ml and a coefficient of variation <5% across the assay range. sST2 was measured by a bedside rapid lateral flow immunoassay (Aspect-PLUS; Critical Diagnostics) with a reporting range of 12.5-257 ng/ml and a coefficient of variation of <10.4% across the assay range [22].

For both NTproBNP and sST2, age- and gender-adjusted upper limits of normal and hence cut-off values were used. This is considered standard in the interpretation of natriuretic peptides. For sST2 a cut-off value of 35 ng/ml has been postulated in previous investigations focusing on the biomarker's prognostic significance [19, 23]. However, previous studies have shown that sST2 levels also significantly depend on age and gender [24]. Therefore, for the purpose of this study, the age- and gender-adjusted 97.5th percentiles of sST2 as measured in a normal population, ranging from 33.2 to 47.6 ng/ml, were used as our upper limit of normal and hence cut-off values for sST2 (table 1) [24, 25].

Statistics

Continuous data are expressed as mean ± standard deviation when normally distributed and as median ± interquartile range if not normally distributed. Categorical data are given as absolute numbers and percentages (%). If the number of values studied for a certain variable greatly differed from the total number of participants, additional information on numbers included is provided.

Participants were divided into four groups according to their biomarker-status, hence the con- or discordancy of sST2 and NTproBNP: group 1 with both biomarkers in physiological ranges below a participant's individual upper limit of normal, group 2 with normal NTproBNP, but pathological sST2 levels, group 3 with pathological NT-proBNP, but normal sST2 and group 4 with pathological values for both biomarkers. For comparison between groups, Kruskal-Wallis, Mann-Whitney, chi-square or analysis of variance (ANOVA) tests were performed accordingly. Spearman correlation coefficients were used to describe linear correlations between sST2 and different variables. Linear and multiple regression coefficients were calculated to represent the linear regression of different variables to sST2 values. The level of significance was set at a p-value of <0.05. All statistical analyses were performed using SPSS® software (version 25.0, SPSS Inc., Chicago, Illinois).

Results

A total of 297 patients were included in the study. The median age was 74 ± 19 years and 41.8% were women. Overall, 89% of patients had known cardiac disease prior to study involvement, leaving 11% of patients undergoing screening or an initial consultation for heart disease. The median values of sST2 and NTproBNP of the whole population were 35.3 ± 32.2 ng/ml and 502 ± 1525 pg/ml, respectively. NTproBNP and sST2 levels were pathological in 55.6% and 36.7% of patients, respectively; 46.5% of patients demonstrated discordant values (one of the biomarkers being in normal and the other in pathological ranges), which are represented in groups 2 and 3. Of interest, 13.8% of patients had normal NTproBNP levels in the presence of elevated sST2 levels (group 2).

Figure 1 demonstrates median sST2 and NTproBNP values according to the biomarker groups, highlighting the discordant pattern of the two biomarkers among the four groups. Clinical (table 2) as well as laboratory and echocardiographic (table 3) findings demonstrate the following main between-group differences:

- In patients with normal NTproBNP levels (groups 1 and 2), those with additional sST2 elevation (group 2) showed significantly higher rates of coronary artery disease (41.5% vs 22%, p = 0.021), peripheral vascular disease (17.1% vs 3.3%, p = 0.006), advanced renal dysfunction (chronic kidney disease stage III/IV; 20.5% vs 10.3%, p = 0.027) as well as higher EuroScore II mortality risks (1.9% vs 1%, p = 0.005).
- In patients with elevated NTproBNP (groups 3 and 4), patients with additional elevation of sST2 (group 4) had more clinical signs of decompensated heart failure, higher EuroScore II mortality risk (1.8% and 3.1%, p = 0.021) and more often suffered from diabetes and cancer. However, there was no statistically significant difference in the percentage of participants with heart failure with reduced, mid-range or preserved ejection fraction in the two groups.
- Despite the statistically significant difference in the sST2 levels of the two groups with pathological sST2 (group 2 58.9 ± 21.6 ng/ml, group 4 63.7 ± 30.3 ng/ml, p = 0.034), these values were rather similar in absolute terms considering the much sicker patient population in group 4. Compared with group 2, participants in group 4 showed more clinical signs of decompensated heart failure, significantly higher rates of heart failure with reduced and preserved ejection fraction, and the prevalence of coronary artery disease, valvular heart disease and diabetes was significantly higher. Also, group 4 participants had suffered more prior heart surgery, had a significantly higher EuroScore II mortality risk and showed worse cardiac function on echocardiography. In addition, group 4 showed a higher frequency of atrial fibrillation and worse renal function.
- Comparison of the two discordant biomarker groups 2 (isolated elevation of sST2) and 3 (isolated elevation of NTproBNP) showed that participants in group 3 more often suffered from heart disease (i.e., atrial fibrillation (14.6% vs 50.5%, p = 0.000) and valvular heart disease (22.5% vs 42.3%, p = 0.029)), had undergone more cardiac interventions (cardiac device implantation (4.9% vs 18.6%, p = 0.037), prior structural heart intervention (14.6% vs 34.0%, p = 0.021)) and showed significantly worse left ventricular function (left ventricular ejection fraction 63.0 ± 8.0% vs 58.0 ± 20.0%, p = 0.005, left ventricular diastolic dysfunction 30.3% vs 81.6%, p <0.001) and larger left atrial volumes (LAVi 33.5 ± 13.8 ml/m^2 vs 49.2 ± 21 ml/m^2, p <0.001) than patients with isolated increased sST2 levels. Additionally, the rate of participants with HFrEF and HFpEF was significantly higher in group 3 compared with group 2 (0% vs 13.6%, p = 0.015, and 0% vs 28.3%, p = 0.001, respectively).

The linear correlation of sST2 with cofactors was less wide and less strong compared with NTproBNP (table

Table 1: Reference limits for sST2 levels (in ng/ml) according to age and sex.

Age group, years	Men, percentile				Women, percentile			
	2.5th	50th	**97.5th**	99th	2.5th	50th	**97.5th**	99th
Empirical reference limits								
35–44	10.6	22.9	**47.6**	49.3	10.4	17.1	**33.2**	45.9
45–54	11.5	22.3	**43.7**	64.4	9.8	17.7	**30.7**	36.7
55–64	12.4	22.7	**43.3**	46.4	9.9	17.5	**34.3**	39.3
65–74	13.2	24.5	**45.2**	54.7	9.3	19.2	**45.1**	53.0
Quantile regression reference limits								
35–44	10.3	21.3	46.5	46.7	10.2	16.6	29.4	29.5
45–54	11.2	22.0	45.8	48.7	10.0	17.2	31.2	34.0
55–64	12.1	22.8	45.2	50.8	9.8	17.8	33.2	39.3
65–74	13.1	23.6	44.6	53.0	9.6	18.5	35.3	45.3

Values used as upper limits of normal in this study are bold. (Adapted from Biaggi et al. Soluble ST2 – a new biomarker in heart failure. Cardiovasc Med. 2019;22:w02008 [25].)

4) and generally weak: all variables except for creatinine showed R coefficients <0.3. In linear regression analyses, the strongest dependency of sST2 was found with EuroScore II mortality risk. Renal function and left atrial volume were identified as significant predicators of sST2 as well. However, R square was low for all tested independent variables, representing a weak predictive accuracy of said variables for sST2. In multiple regression analysis, left atrial volume was the strongest independent predictor of sST2 elevation, while glomerular filtration rate was non-significant as an independent predictor of sST2 (Table 5). However, glomerular filtration rate turned out to be a significant independent predictor of sST2 when compared with the two variables Euro Score II and LAVi in multiple regression analysis (R = −0.275; 95% confidence interval [CI] −0.483, −0.067; p = 0.010), although NTproBNP showed decisively stronger dependency on renal function (R = −63.430; 95% CI −90.554, 36.307; p <0.001) than sST2.

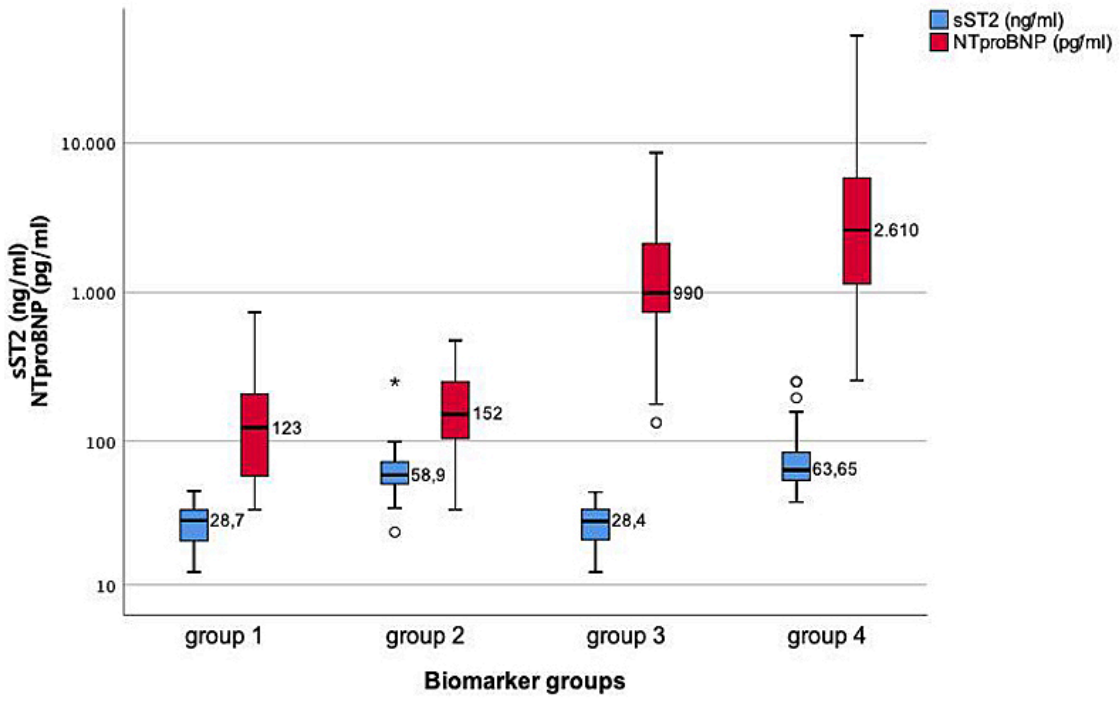
Discussion

Soluble ST2 has been proven to be a useful biomarker in the prognosis and monitoring of acute and chronic heart failure patients, but its use in daily practice is less well studied. In this cross-sectional cohort we studied sST2 levels in comparison with NTproBNP in a heterogeneous outpatient all-comer population. We have two main findings. Firstly, in patients with elevated natriuretic peptides, elevation of sST2 was associated with clinical signs of decompensated heart failure. Secondly, sST2 was elevated in a high percentage of study participants with physiological NTproBNP levels, implying a separate pathway of sST2 secretion.

The first finding might indicate a potential added value of measuring sST2 in addition to NTproBNP in clinical practice. Soluble ST2 serves as a strong prognostic and monitoring tool in acute and chronic heart failure [16–18]. However, the diagnostic value of sST2 in heart failure has been described as inferior to that of natriuretic peptides and therefore sST2 has not been promoted as a diagnostic biomarker [14]. In our study, elevation of both NTproBNP and sST2 as opposed to isolated elevation of NTproBNP was associated with higher EuroScore II mortality risk as well as more frequent clinical signs of decompensated heart failure. Therefore, in patients with elevated NTproBNP and ambiguous signs of decompensated heart failure, additional measurement of sST2 may help identify those with decompensated heart failure and thus stratifying individual risk and prognosis. This may be particularly important in patients suffering from impaired renal function or atrial fibrillation, comorbidities strongly influencing NTproBNP levels [6, 8, 9]. Of importance, sST2 levels in the sickest population (group 4) were similar to those of group 2 (healthier participants without heart failure), underlining the limited diagnostic power of sST2 when used independently from NTproBNP.

The second main finding was the fairly high percentage of participants showing isolated sST2 elevation, raising the question of the meaning of elevated sST2 in the absence of acute or chronic heart failure. Based on the results of this study, several assumptions regarding the pathway of sST2 can be made. Firstly, sST2 may represent vascular disease in addition to heart failure [26–28], as the presence of vascular disease was the main difference between groups 1 and 2. If a relevant part of kidney disease is assumed to be of vascular origin, this might also explain the lower kidney function of group 2 compared with patients of group 1. Of note, we and others [29] could show that glomerular filtra-

Figure 1: Median levels of sST2 and NTproBNP in the four biomarker groups and their discordance. Group 1 = both biomarkers normal, group 2 = isolated sST2 elevation, group 3 = isolated NTproBNP elevation, group 4 = both biomarkers pathological.



tion rate itself is a weak (but significant) independent predictor of sST2. The interplay of atherosclerosis, renal function and sST2 levels merits more thorough exploration in the future. Secondly, elevation of sST2 was reported in patients with various clinical conditions such as diabetes, active cancer and unspecific elevation of C-reactive protein, supporting an assumption that chronic inflammation might be an important pathway of sST2 elevation [24, 30–32]. Thirdly, previous studies have come to the conclusion that the sST2 pathway is induced by mechanical strain in cardiac fibroblasts and myocytes [13]. Our results support this finding, as left atrial volume was the strongest independent predictor of elevated sST2. We conclude that there must be several and not fully understood pathways of sST2 generation, and further studies are necessary to analyse what elevated sST2 levels truly stand for.

Finally, we would like to address the subject of the cut-off level for sST2. In this study we used the age- and gender-adjusted 97th percentile as sST2's upper limit of normal [24]. Most chronic heart failures studies postulated an sST2 cut-off value of around 35 ng/ml to predict worse prognoses in heart failure patients [33, 34]. However, for

Table 2: Comparison of clinical variables and patient history in the four biomarker groups.

Variable	Group 1	Group 2	p-value Gr. 1-2	Group 3	Group 4	p-value Gr. 3-4	p-value Gr. 2-4
	Normal sST2, Normal NT-pBNP (n = 91)	Pathol. sST2, Normal NT-pBNP (n=41)		Normal sST2, Pathol. NT-pBNP (n = 97)	Pathol. sST2, Pathol. NT-pBNP (n = 68)		
Clinical assessment							
Age (years)	68 (±22)	67 (±20)	0.350	75 (±16)	78 (±17)	0.158	**0.011**
Gender (female)	42 (46.2%)	13 (31.7%)	0.119	46 (47.4%)	23 (33.8%)	0.081	0.066
BMI (kg/m^2)	24.9 (±6.3)	24.8 (±9.2)	0.731	25.9 (±6.3)	24.95 (±5.1)	0.565	0.743
MAP (mm Hg)	95 (±17.5)	95 (±17.8)	0.606	94.7 (±18.1)	93 (±17)	0.301	0.592
HR (1/min)	66 (±11)	66 (±14)	0.683	70 (±17)	76 (±28)	***0.002***	**<0.001**
Positive HJR (n = 112)	0 (0%)	0 (0%)	N/A	10 (27.8%)	17 (51.5%)	***0.044***	**<0.001**
Leg oedema (n = 190)	4 (6.8%)	4 (15.4%)	0.211	11 (18.6%)	22 (47.8%)	***0.001***	**<0.001**
Pulmonary rattling sounds (n = 123)	0 (0%)	2 (10.5%)	***0.037***	4 (12.1%)	13 (41.9%)	***0.007***	**<0.001**
Orthopnoea (n = 120)	1 (2.8%)	1 (3.8%)	0.814	6 (16.7%)	4 (18.2%)	0.882	0.255
NYHA I	47 (54.7%)	22 (55%)	0.256	31 (32.6%)	19 (28.8%)	0.496	**0.034**
NYHA II	30 (34.9%)	10 (25%)	0.256	44 (46.3%)	26 (39.4%)	0.496	**0.034**
NYHA III	9 (10.5%)	7 (17.5%)	0.256	19 (20%)	20 (30.3%)	0.496	**0.034**
NYHA IV	0 (0%)	1 (2.5%)	0.256	1 (1.1%)	1 (1.5%)	0.496	**0.034**
NYHA ≥III	9 (10.5%)	8 (20%)	0.145	20 (21.1%)	21 (31.8%)	0.123	**0.024**
Chest pain (n = 212)	24 (31.6%	14 (38.9%)	0.445	11 (19.6%)	3 (8.8%)	0.170	**0.015**
History							
EuroScore II (%)	1.0 (±0.8)	1.9 (±2.0)	***0.005***	1.8 (±2.1)	3.1 (±3.6)	***0.021***	**0.003**
Heart disease present	71 (78%)	36(87.8%)	0.184	94 (96.9%)	64 (94.1%)	0.382	0.334
HFrEF*	0 (0%)	0 (0%)	N/A	12 (13.6%)	15 (24.6%)	0.088	**<0.001**
HFmrEF†	0 (0%)	0 (0%)	N/A	2 (4.3%, n = 46)	2 (5.7%, n = 35)	0.779	0.237
HFpEF‡	0 (0%)	0 (0%)	N/A	13 (28.3%, n = 46)	9 (25.7%, n = 35)	0.799	**0.005**
Any disease present	80 (87.9%)	36 (87.8%)	0.986	96 (99%)	68 (100%)	0.401	**0.024**
Prior heart surgery	10 (11%)	9 (22%)	0.097	24 (24.7%)	23 (33.8%)	0.203	**0.028**
Prior SHD intervention	12 (13.2%)	6 (14.6%)	0.823	33 (34%)	23 (33. 8%)	0.979	0.071
≥ moderate valvular HD	24 (26.7%)	9 (22.5%)	0.614	41 (42.3%)	36 (53.7%)	0.148	**0.003**
Hypertension	41 (45.1%)	21 (51.2%)	0.511	60 (61.9%)	41 (60.3%)	0.839	0.569
Atrial fibrillation	10 (11%)	6 (14.6%)	0.553	49 (50.5%)	41 (60.3%)	0.214	**<0.001**
Coronary artery disease	20 (22%)	17 (41.5%)	***0.021***	35 (36.1%)	34 (50%)	0.074	**0.007**
Prior myocardial infarction	10 (11%)	6 (14.6%)	0.553	12 (12.4%)	10 (14.7%)	0.664	0.760
Prior PCI	14 (15.4%)	13 (31.7%)	***0.031***	26 (26.8%)	21 (30.9%)	0.568	0.162
Cardiac electronic devices	3 (3.3%)	2 (4.9%)	0.660	18 (18.6%)	19 (27.9%)	0.155	**0.001**
Cardiomyopathy	6 (6.6%)	2 (4.9%)	0.702	11 (11.3%)	10 (14.7%)	0.523	0.212
Diabetes mellitus	12 (13.2%)	5 (12.2%)	0.875	11 (11.3%)	18 (26.5%)	***0.012***	**0.017**
COPD GOLD ≥III	1 (1.1%)	0 (0%)	0.500	2 (2.1%)	1 (1.5%)	0.780	0.721
Liver cirrhosis	0 (0%)	0 (0%)	N/A	0 (0%)	2 (2.9%)	0.089	**0.034**
Prior stroke/TIA	2 (2.2%)	3 (7.3%)	0.154	12 (12.4%)	6 (8.8%)	0.472	0.930
PVD	3 (3.3%)	7 (17.1%)	***0.006***	10 (10.3%)	4 (5.9%)	0.315	0.072
Active cancer	3 (3.3%)	2 (4.9%)	0.660	2 (2.1%)	10 (14.7%)	***0.002***	**0.001**
Past cancer	9 (9.9%)	2 (4.9%)	0.335	16 (16.5%)	8 (11.8%)	0.396	0.317
Prior radiotherapy	4 (4.4%)	1(2.4%)	0.586	7 (7.2%)	3 (4.4%)	0.457	0.640
Prior chemotherapy	3 (3.3%)	1 (2.4%)	0.790	6 (6.2%)	3 (4.4%)	0.621	0.801
On any CHF medication	48 (52.7%)	25 (61%)	0.379	82 (84.5%)	57 (83.8%)	0.902	**0.020**

BMI = body mass index; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease; EF = ejection fraction; HD = heart disease; HF = heart failure; HJR = hepatojugular reflux; HR = heart rate; MAP = mean arterial pressure; NYHA = new York heart Association; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease; SHD = structural heart disease; TIA = transient ischaemic attack All continuous variables presented as median ± interquartile range, unless stated otherwise. Group 1 = both biomarkers normal, group 2 = pathological sST2, group 3 = pathological NTproBNP, group 4 = both biomarkers pathological. * HFrEF: EF<40% and HF symptoms. † HFmrEF: EF 40–49%, HF symptoms, pathological NTproBNP, diastolic dysfunction. ‡ HFpEF: EF ≥50%, HF symptoms, pathological NTproBNP, diastolic dysfunction

Table 3: Comparison of laboratory and echocardiographic variables in the four biomarker groups

Variable	Group 1	Group 2	p-value Gr. 1-2	Group 3	Group 4	p-value Gr. 3-4	P-value Gr. 2 - 4
	Normal sST2, normal NTproBNP (n = 91)	Pathol. sST2, normal NTproBNP (n = 41)		Normal sST2, pathol. NT-proBNP (n = 97)	Pathol. sST2, pathol. NTproBNP (n = 68)		
Laboratory results							
Hb (g/l, mean ± SD)	139.1 (±14.4)	137.8 (±15.2)	0.712	131.9 (±15.1)	128.3 (±18.3)	0.198	**0.009**
Anaemia (Hb <130 g/l)	9 (11.7%)	8 (21.6%)	0.250	21 (26.9%	23 (39.7%)	0.275	**0.034**
GFR CKD-EPI (ml/min)	88.0 (±20.2)	78.8 (±30.5)	***0.018***	68.8 (±31.5)	63.3 (±42.8)	0.053	**0.004**
Creatinine (µmol/l)	71.5 (±20.3)	81.0 (±23.0)	***0.002***	81.5 (±32.0)	95.0 (±68.0)	**0.017**	**0.047**
CKD grade III (eGFR 30–60 ml/min)	9 (10.3%)	5 (12.8%)	***0.027***	25 (27.2%)	18 (26.9%)	0.095	**0.002**
CKD grade IV (eGFR <30 ml/min)	0 (0%)	3 (7.7%)	***0.027***	5 (5.4%)	11 (16.4%)	0.095	**0.002**
GPT/ALT (U/l)	21.5 (±13.3)	28.0 (±27.8)	0.389	19.0 (±14.0)	19.0 (±13.0)	0.375	0.384
GOT/AST (U/l)	18.0 (±8.3)	21.5 (±19.3)	0.162	21.0 (±6.0)	22.0 (±15.0)	0.503	0.855
CRP (mg/l)	0.6 (±2.2)	1.2 (±4.6)	0.435	2.2 (±5.5)	5.5 (±13.2)	**0.008**	**0.001**
Leucocytes (G/µl)	6.4 (±1.8)	5.9 (±2.8)	0.730	6.7 (±2.4)	6.5 (±2.9)	0.790	0.338
LDH (U/l)	167.0 (±55.0)	166.0 (±31.0)	0.922	211.0(±98.3)	206.0 (±89.0)	0.492	**0.048**
LDL (mmol/l)	2.8 (±1.4)	2.3 (±1.1)	***0.038***	2.5 (±1.8)	2.2 (±1.2)	0.581	0.514
Echocardiography							
LVEF (%)	63.7 (±11.2)	63.0 (±8.0)	0.476	58.0 (±20.0)	53.3 (±22.3)	**0.022**	**<0.001**
Normal LV function (EF ≥50%)	83 (92.2%)	36 (92.3%)	0.789	68 (71.6%)	41 (62.1%)	0.091	**<0.001**
Moderate LV function (EF 30–50%)	6 (6.7%)	3 (7.7%)	0.789	23 (24.2%)	16 (24.2%)	0.091	**<0.001**
Poor LV function (EF <30%)	1 (1.1%)	0 (0%)	0.789	4 (4.2%)	9 (13.6%)	0.091	**<0.001**
LV EDVi (ml/m^2)	52.1 (±21.7)	56.0 (±21.4)	0.578	60.0 (±28.7)	60.4 (±35.2)	0.304	0.512
Diastolic dysfunction	20 (29%)	10 (30.3%)	0.891	40 (81.6%)	31 (81.6%)	0.995	**<0.001**
LAVi (ml/m^2)	32.9 (±11.3)	33.5 (±13.8)	0.680	49.2 (±21.0)	49.6 (±22.0)	0.846	**<0.001**
Normal RV function (FAC ≥35%)	74 (92.5%)	29 (90.6%)	0.742	67 (78.8%)	36 (64.3%)	0.057	**0.001**
RV/RA P-gradient (mm Hg)	22.3 (±8.3)	22.1 (±8.0)	0.681	26.6 (±12.6)	31.0 (±11.2)	0.330	**0.001**

CKD = chronic kidney disease; CRP = C-reactive protein; (e)GFR = (estimated) glomerular filtration rate; EPI = Chronic Kidney Disease Epidemiology Collaboration; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GOT/AST = glutamic oxaloacetic transaminase / aspartate aminotransferase; GPT/ALT = glutamic pyruvic transaminase / alanine aminotransferase; Hb = haemoglobin; LAVi = left atrial volume index; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LV = left ventricular; LV EDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; RV =right ventricular; RV/RA P-gradient = right ventricular to right atrial pressure gradient; SD = standard deviation All continuous variables presented as median ± interquartile range, unless stated otherwise. Group 1 = both biomarkers normal, group 2 = pathological sST2, group 3 = pathological NTproBNP, group 4 = both biomarkers pathological.

Table 4: Linear correlations between NTproBNP, sST2 and other variables.

Variable	Spearman's correlation with NTproBNP (R coefficient)	p-value (NTproBNP)	Spearman's correlation with sST2 (R coefficient)	p-value (sST2)
LAVi	0.651	***<0.001***	0.199	***<0.001***
EuroScore II	0.622	***<0.001***	0.280	***<0.001***
GFR	−0.591	***<0.001***	−0.259	***<0.001***
Age	0.531	***<0.001***	0.179	***0.002***
RV/RA P-gradient	0.526	***<0.001***	0.196	***0.006***
CRP	0.408	***<0.001***	0.248	***<0.001***
Creatinine	0.407	***<0.001***	0.334	***<0.001***
Hb	−0.392	***<0.001***	−0.098*	0.123
LVEF	−0.375	***<0.001***	−0.159	***0.007***
HR	0.304	***<0.001***	0.173	***0.003***
RV FAC	0.247	***<0.001***	0.213	***<0.001***
GPT/ALT	−0.201	***0.027***	0.095*	0.301
LV EDVi	0.145	***0.015***	0.024*	0.686
GOT/AST	0.120*	0.248	0.196*	0.059
MAP	−0.114*	0.054	−0.056 *	0.347
Leucocytes	0.100*	0.116	0.060*	0.348
LDL	0.062*	0.484	−0.161*	0.070
BMI	0.006*	0.917	0.024*	0.681

BMI = body mass index; CRP = C-reactive protein; Hb = haemoglobin; HR = heart rate; LAVi = left atrial volume index; LV EDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; RV = right ventricular; RV/RA P-gradient = right ventricular to right atrial pressure gradient * non-significant correlation, p >0.05

many patients this cut-off level is substantially lower than the age- and gender-adjusted upper limit of normal. Therefore, studies focusing on the prognostic significance of sST2 in acute heart failure have been using higher sST2 values as cut-off for risk stratification [35]. If the 35 ng/ml cut-off value had been used in our study, the group with isolated sST2 elevation would have been even larger (19.9% vs 13.8% of all participants), but there would have been no difference regarding vascular disease in this group compared with those with no elevation of biomarkers. In addition, when using the cut-off of 35 ng/ml, 8% of patients with no diagnosed cardiac disease, signs or symptoms would have showed pathological sST2 levels, compared with 3% when using age- and gender-adjusted cut-off values. This study's data underline the necessity of using the age- and gender-adjusted 97th percentile as sST2's upper limit of normal when measuring sST2 in a heterogeneous, out-patient population for mere diagnostic purposes. Alternatively, one could argue that measuring sST2 in a partly healthy population is inefficient on the whole and does not lead to significant prognostic or diagnostic conclusions [36].

Limitations

In this study we used a bedside test instead of an ELISA method for measuring sST2, with a coefficient of variation that has been reported higher for bedside testing than that typically expected for an immunoassay test. Since we did not use both test methods and compare the respective results, we cannot exclude an influence of the test method used on sST2 levels and thus the distribution of our groups. Further comparison between the two test methods is necessary to understand relevant differences. Both diagnostic tests, however, rely on the same method of detecting sST2 via an enzyme-linked immunosorbent assay. The development of alternative testing methods is necessary to truly interpret sST2 plasma concentrations and their relevance.

In order to characterise our population by a well-known risk model combining several clinical important variables, we have calculated EuroScore II risk for each participant. Seeing that this risk model was developed and validated for the calculation of mortality risk after cardiac surgery, the significance of its interpretation in this population may be limited.

This study was not designed to collect any follow-up data, hence the prognostic value of sST2 compared with NT-proBNP could not be evaluated.

Because of the study design, calculation of the predictive significance of categorical variables on sST2 levels was not practicable. This could be subject of further studies.

Conclusion

In an all-comer cardiology outpatient clinic, the added clinical value of sST2 measurements in addition to NTproBNP was limited. Elevated sST2 levels corroborated clinical signs of heart failure in patients with elevated NTproBNP. However, a surprisingly high number of participants showed isolated elevation of sST2 levels, pointing to an additional pathway of sST2 elevation independent of heart failure. Although measuring sST2 in addition to NTproBNP may be helpful in patients with uncertain signs of heart failure or in patients with confounding factors for the elevation of NTproBNP, routine measurement of sST2 in a general cardiology population cannot be promoted based on this study.

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Table 5: Linear and multiple regression between sST2 and linear variables.

	Linear univariate regression with sST2				Multiple regression between sST2 and variables with statistically significant univariate linear regression (Adjusted R^2 = 0.264)		
Variable	**Unstandardised coefficient**	**R^2**	**95% CI**	**p-value**	**Unstandardised coefficient**	**95% CI**	**p-value**
Euro Score II	2.978	0.051	1.458, 4.498	***<0.001***	0.838	−1.703, 3.379	0.515
RV FAC	−0.611	0.042	−0.986, -0.236	***0.002***	−0.299	−0.886, 0.289	0.316
CRP	0.519	0.038	0.139, 0.899	***0.008***	0.611	0.013, 1.208	0.045
Hb	−0.494	0.054	−0.751, −0.236	***<0.001***	0.019	−0.389, 0.427	0.926
LAVi	0.387	0.078	0.225, 0.548	***<0.001***	0.517	0.174, 0.859	***0.003***
GFR CKD-EPI	−0.386	0.063	−0.560, −0.212	***<0.001***	−0.121	−0.737, 0.494	0.697
HR	0.368	0.036	0.148, 0.589	***0.001***	−0.016	−0.437, 0.405	0.940
LVEF	−0.354	0.022	−0.626, −0.083	***0.011***	−0.136	−0.632, 0.360	0.588
Age	0.27	0.015	0.016, 0.524	***0.037***	−0.233	−0.778, 0.311	0.398
Creatinine	0.183	0.082	0.111, 0.254	***<0.001***	0.070	−0.130, 0.271	0.490
LDL	−2.25	0.013	−5.688, 1.189	0.198			
Leucocytes	1.808	0.011	−0.331, 3.947	0.097			
BMI	0.691	0.011	−0.059, 1.440	0.071			
GOT/AST (U/l)	0.666	0.029	−0.019, 1.35	0.056			
RV/RA P-gradient	0.182	0.006	−0.139, 0.503	0.265			
MAP	−0.179	0.007	−0.422, 0.063	0.146			
GPT/ALT (U/l)	0.145	0.003	−0.365, 0.654	0.575			
LV EDVi	0.08	0.006	−0.039, 0.200	0.188			

BMI = body mass index; CI = confidence interval; CKD = chronic kidney disease; CRP = C-reactive protein; Hb = haemoglobin; HR = heart rate; LAVi = left atrial volume index; LV EDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; MAP = mean arterial pressure; RV = right ventricular; RV/RA P-gradient = right ventricular to right atrial pressure gradient

PB and CA by Ruwag Handels AG, Bettlach for a presentation on this subject in September 2018.

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